Clinical safety testing in healthy volunteers

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Overview

- Regulatory view of clinical safety testing
  - Audiences and goals
  - FDA perspective
- Designing clinical safety studies
  - Requirements and challenges under the Animal Rule
  - Ethical issues
  - Sample size
  - Study population
  - Safety evaluations
  - Dose and regimen selection
  - Data capture and analysis
- Post-approval safety assessment

Key points

- Animal Rule requires clinical safety trials
- FDA review focuses on risk-benefit ratio
- Safety trial design centers on accurate risk description and potential population

Audiences for safety data

- Patients
- Providers
- Public health community
- Regulatory agencies
- Therapeutic development community
- Public policy community

Goals of safety evaluation

- Risk description (nature, incidence)
  - Animal toxicology
  - Structured clinical safety studies
- **Risk/benefit assessment**
- Risk management
  - Identification of risk factors for adverse events (AEs)
  - Risk mitigation
- Risk communication
  - Product labeling (e.g., Black Box warning)
  - Investigator's brochure
  - Dear Doctor letter, FDA advisories

Factors in risk-benefit assessment

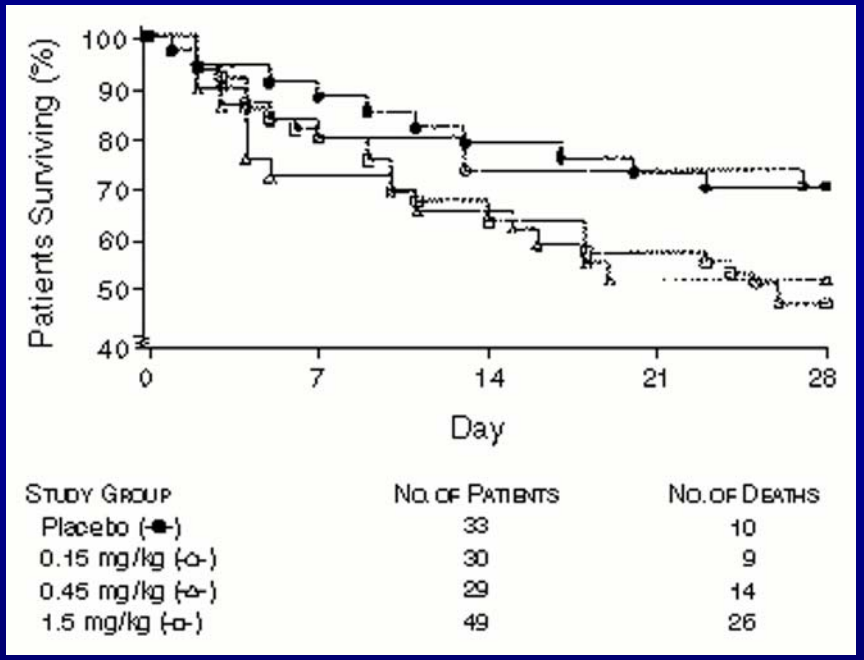
- Intended use
- Estimate of treatment benefit
- Potential population exposure
- Adequacy of safety database to describe risk in real-world population
- Risks of other products for same disease
- Risks of similar compounds
- Ability of labeling to communicate risk

Issues in risk-benefit assessment

- Greater risks require greater benefits
- Risks may change
  - New risks emerge in new populations
  - Rare risks emerge in larger populations
- Benefits may change
  - Benefits may decrease in sicker patients
  - Benefits may decrease in less sick patients
  - Efficacy (trials) ≠ effectiveness (real world)

TNFR fusion protein in septic shock

- **Effective in animals**
- **Safe in healthy subjects**
- **↑ mortality in patients**



Study Group	No. of Patients	No. of Deaths
Placebo (-●-)	33	10
0.15 mg/kg (-○-)	30	9
0.45 mg/kg (-△-)	29	14
1.5 mg/kg (-□-)	49	26

Fischer CJ *et al*. NEJM 1996; 334:1697

FDA safety review

- Sources of data
  - Controlled trials
  - Uncontrolled trials
  - Case reports
- Safety population
  - Size
  - Demographics
  - Medical characteristics
  - Control group
- Extent of exposure
  - Number of doses
  - Duration of dosing
  - Dose range
  - Exposure range (e.g., AUC)
- Clinical adverse events
  - Deaths/Serious AEs (SAEs)
  - Discontinuations
  - Nonserious AEs
  - Incidence, severity
  - Causality
  - Reversibility
  - Subgroup analyses
- Laboratory data
  - Group comparisons
  - Outlier analyses
- Specific risks
  - Immunogenicity
  - Hepatotoxicity
  - QT prolongation
  - Drug interactions

Animal Rule safety requirements

- Safety must be established for approval under the Animal Rule
- Safety established as for non-Animal Rule NDAs/BLAs (21 CFR 314.50 and 601.25)
- Post-marketing safety and efficacy studies required in patients with disease when ethical and feasible

Questions in safety testing

- What should be done when?
- How many subjects should be studied?
- Who should be studied?
- What should the starting dose be?
- How high should the dose go?
- What AEs should be looked for?
- How should the data be analyzed?

Challenges in safety testing

- General
  - Describing risks accurately
  - Detecting rare events
  - Assessing causality
  - Extrapolating to potential real world population
- Animal Rule-specific
  - No benefit to volunteers
  - No drug-disease interaction data
  - No PK/PD data in ill patients
  - Increased uncertainty about risk-benefit

Factors in safety study design

- Ethical issues
  - Informed consent
  - Investigator training
  - IRB approval
- Bias minimization
  - Control group selection
  - Blinding scheme
  - Randomization scheme
- Sample size
  - Potential population
  - Risk-benefit assessment
  - Desired statistical power
- Study population
  - Intended use
  - Potential population
  - Extrapolation to real world
- Planned evaluations
  - History/physical/laboratory
  - Pharmacokinetics
  - Immunogenicity
- Dose/regimen selection
  - NOAEL
  - PAD
  - PK/PD

Ethical considerations

- No benefit to healthy volunteers
  - Occurs in other development programs (e.g., anti-infectives)
  - Risk minimization is critical
- Written informed consent is central
- Rigorous investigator training
  - Subject protection
  - Good Clinical Practices
  - Protocol
- IRB approval
- DMC may be helpful in some settings

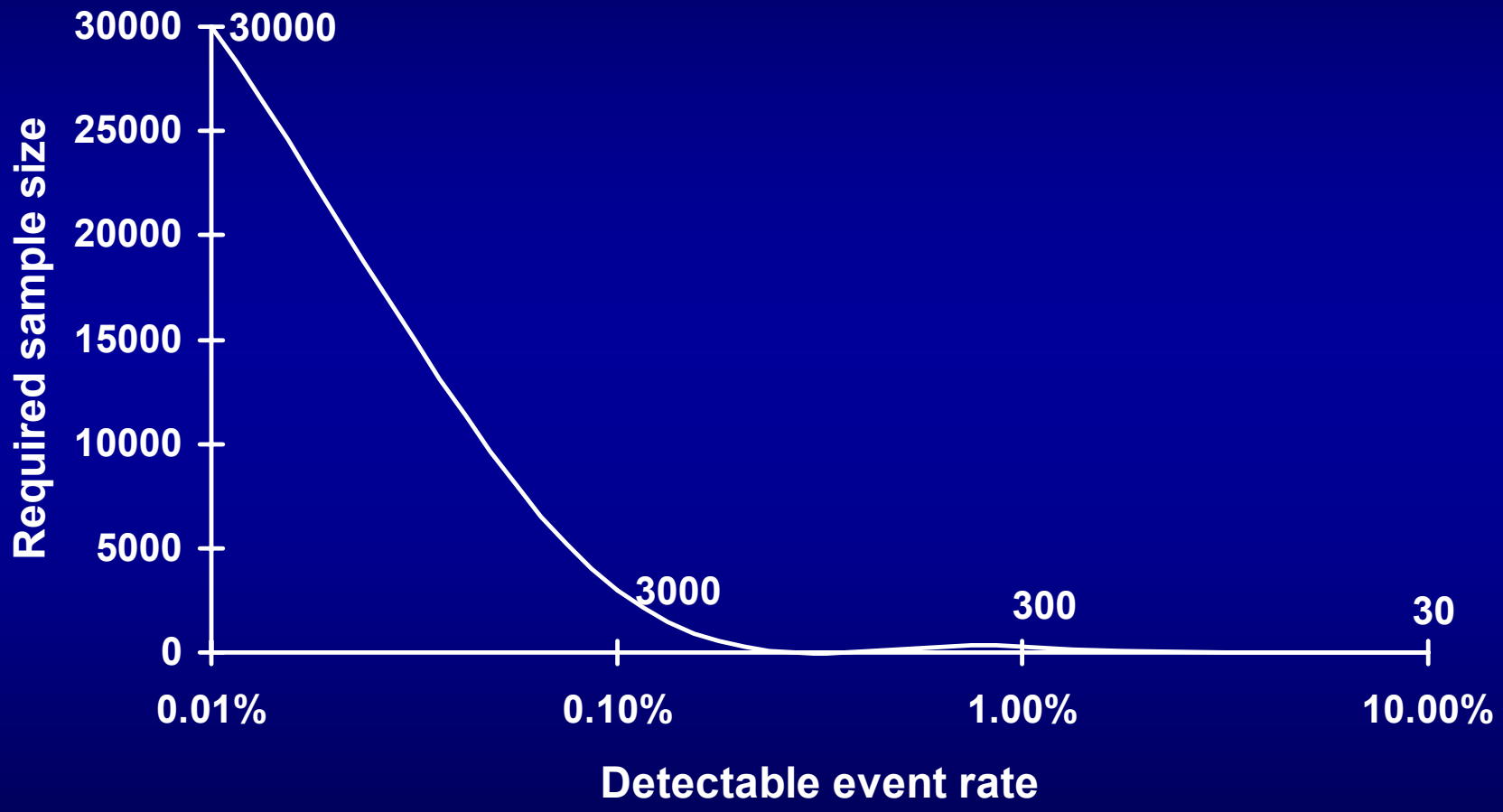
Bias minimization in safety studies

- Potential mechanisms for entry of bias
  - Subjective assessments of adverse events
  - Incomplete information
  - Different manifestations of same AE
  - Overlapping manifestations of different AEs
  - Different etiologies for same AE
  - Temporal variability in AE occurrence
  - Variation in estimates of incidence rates
- Measures to minimize bias
  - Concurrent placebo control group
  - Randomization
  - Blinding
  - Prespecified safety definitions/evaluations
  - Good Clinical Practices

Clinical safety sample size in Animal Rule development

- Who and how large is the intended population?
  - A few sick patients? (e.g., Oct. 2001 anthrax patients)
  - Many sick patients? (e.g., mass casualty)
  - Many healthy subjects? (e.g., prophylaxis)
- What serious event rate is clinically acceptable?
  - Larger benefit may support higher risk
  - Lower risks may be unacceptable if they outweigh benefit
  - 0.1% mortality rate x 100,000 subjects = 100 deaths
  - Acceptable risk may depend on risk/benefit of other treatments
- What sample size is required to exclude that rate?
  - Rule of 3 – Exclusion of an event rate ≥1/N with 95% confidence requires a sample size of ~3N
  - Caveats:
    - Assumes background event rate << 1/N
    - N ≥ 20
    - Extrapolation to population requires representative sample

Rule of 3


30000
25000
20000
15000
10000
5000
0
Required sample size
30000
3000
300
30
0.01%
0.10%
1.00%
10.00%
Detectable event rate

Pavlizumab-associated AEs

Adverse event	Pavlizumab (N=1002)	Placebo (N=500)	Nominal p-value*
URI	52.6%	49.0%	0.21
Otitis media	41.9%	40.0%	0.50
Rhinitis	28.7%	23.4%	0.03
Rash	25.6%	22.4%	0.18
Pain	8.5%	6.8%	0.26
Hernia	6.3%	5.0%	0.35
SGOT increased	4.9%	3.8%	0.36
Pharyngitis	2.6%	1.4%	0.19

*Two-tailed χ^2 test; no correction for multiple comparisons

Sample sizes needed for 2-arm studies to detect differences in event rates*

Differences in event rates	Total N
20% vs. 25%	2200
1% vs. 2%	5000
3% vs. 4%	11,600
10% vs. 11%	30,000
0.1% vs. 0.2%	50,000

* α = 0.05 (two-sided); power = 80%

Most frequently reported ciprofloxacin-associated SAEs

Event	Cases reported per 10^6 exposures (N ≈ 250,000,000)
Convulsion	0.86
Anaphylactoid reaction	0.67
Rash	0.67
Tendon rupture	0.57
Acute kidney failure	0.56
Tendon disorder	0.51
LFT abnormal	0.48
Thrombocytopenia	0.41
Kidney failure	0.39
Kidney function abnormal	0.39

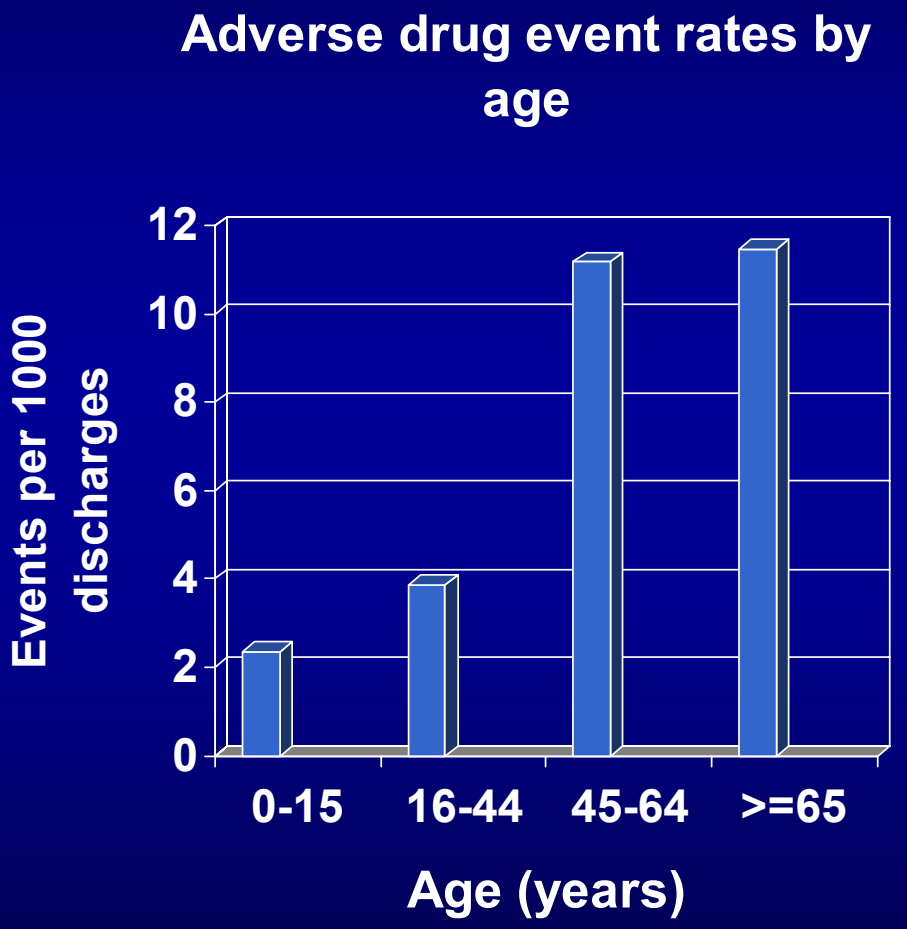
Clinical safety population in Animal Rule development

- No benefit to subjects
  - Even low risks need to be considered carefully
  - Informed consent is central to participation
- Initial studies: healthy volunteers
  - Age 18-65, balanced sex/racial distribution
  - Exclusion criteria
    - Comorbid conditions (↑ risk, may confound assessment)
    - Specific exclusions (e.g., h/o thrombosis in trials of IGIV)
- Later studies:
  - ?Children
  - ?Elderly
  - ?Subjects with co-morbid conditions
  - ?Pregnant/nursing mothers
  - ?Drug interaction studies for small molecules

Adverse drug events in the elderly

Reasons for increased ADE rates in elderly

- Polypharmacy
- Severity of illness
- Comorbidities
- Smaller body size
- ↓ clearance
- Prior drug reactions



Leape LL *et al.* NEJM 1991; 324:377

Gender differences in AE rates

Visual adverse events in telithromycin Phase 3 trials

Gender/ Age	Telithromycin	Controls	Relative risk	Nominal p-value
Female ≤40 y	2.1%	0.0%	22.1	0.0005
Female >40 y	1.0%	0.35%	2.9	0.20
Male ≤40 y	1.2%	0.48%	2.5	0.32
Male >40 y	0.27%	0.33%	0.84	1.0
Total	1.1%	0.28%	3.9	0.0006

Planned evaluations

- Clinical
  - Structured clinical interview
  - Vital signs, physical examination
  - Product-specific (e.g., infusion reactions)
- Laboratory
  - Pharmacokinetics
  - Hematology, chemistry, coagulation parameters, LFTs, U/A
  - Others based on preclinical toxicology (e.g., EKG)
- Immunogenicity (HAMA, HACA, HAHA vs. IGIV, mAbs, other antigens)
  - Neutralization of IGIV, mAb activity
  - Non-neutralizing Abs – alteration of product PK
  - Anaphylaxis
  - Cross-reacting Abs to human tissue
  - Immune complex disease (e.g., serum sickness)
  - Cytokine release
  - Nonspecific binding of polyclonal Abs/mAbs to normal tissues

Effects of immunogenicity

Risk of thrombocytopenia (TCP) after abciximab readministration in relation to human anti-chimeric Ab (HACA) status

Event	HACA (+) before readministration	HACA (-) before readministration	p value
Any TCP (100×10^9/L)	14.1%	4.4%	0.002
Severe TCP (50×10^9/L)	9.9%	2.3%	0.002
Profound TCP (20×10^9/L)	5.6%	1.6%	0.036

Dery J-P *et al.* Am J Cardiol 2004; 93:979

Dose selection/escalation

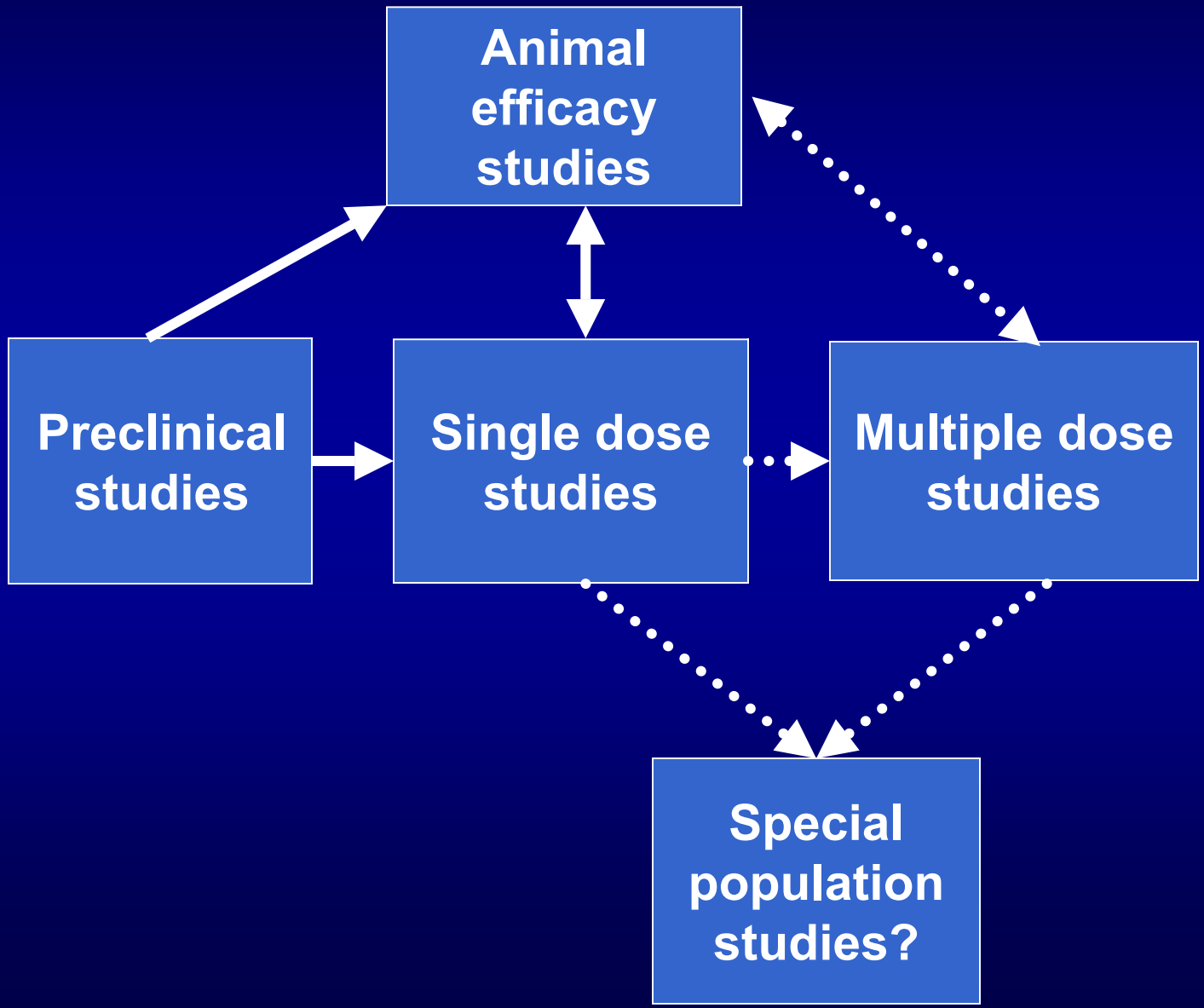
NOAEL + safety factor
(animal studies)
↓
Initial dose
(human studies)
↓
Escalate to maximal tolerated dose (MTD)
(human studies)
↓
Pharmacologically active dose (PAD)
(animal studies):
↓
MTD > PAD (HED)?

NOAEL + safety factor
(animal studies)
↓
Pharmacologically active dose
(animal studies)
↓
Initial dose
(human studies)
↓
Escalate to PAD (HED)
(human studies)
↓
PAD (HED) < MTD?

Dose/regimen escalation

- Preclinical toxicology
- Pharmacologically active dose (animal studies)
- Pharmacokinetics in animals/humans
- Human safety results at lower dose cohorts
- Specific concerns for biologic products
  - Product-specific toxicities (e.g., IGIV infusion reactions)
  - Oncotic load for IGIV
  - Immunogenicity
  - Effects of product quality on safety
    - Aggregates
    - Denatured/degraded protein
    - Excipients/stabilizers
    - Manufacturing reagents (e.g., solvent/detergent for viral inactivation)
    - Plasma protein contamination (e.g., prekallikrein activator)
  - Predictability of dose-toxicity curve

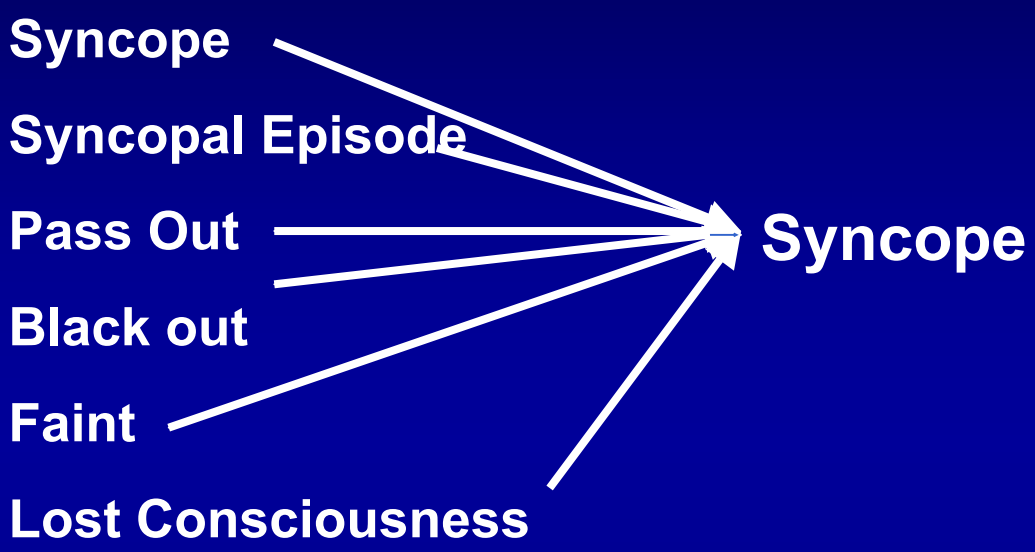
Dose evaluation schema



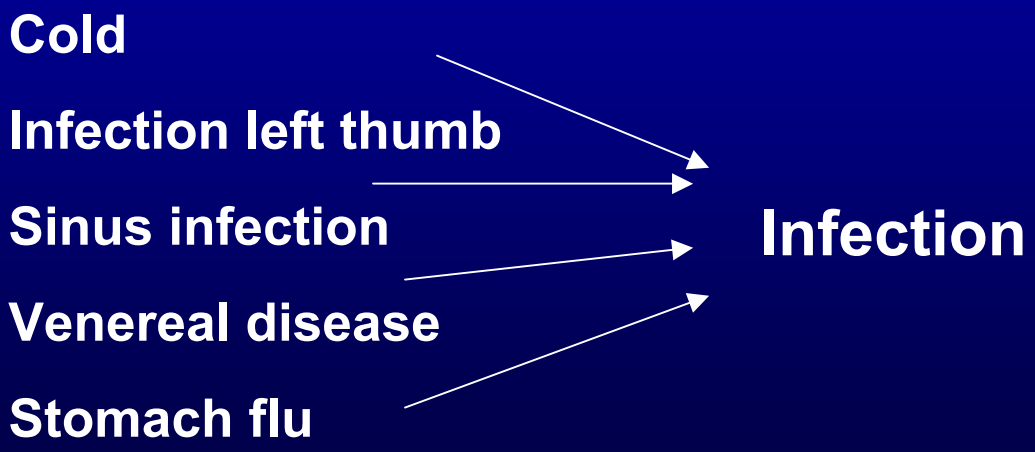
Data capture and reporting

- Structured case report form
- Investigator training
- Controlled safety vocabulary (MedDRA)
- Standardized coding rules
- Standardized severity scale
- Severity scale designed for healthy subjects
- Quality control/quality assurance
- Electronic data submission

Adverse event coding



Ideal



Real

Clinical event analyses

- Deaths, SAEs, Discontinuations due to AEs
  - Incidence rates
  - Narrative details
  - Causality analysis
    - Temporal relationship (latency, duration of SAEs)
    - Dose, pharmacokinetic, immunologic relationships
    - Histopathologic relationship
    - Biologic plausibility
- Nonserious adverse events
  - Incidence rates
  - Subgroup analyses
    - Demographic
    - Comorbidities
    - Concomitant medications
  - Causality analysis
    - Temporal relationship (latency, duration, dechallenge, rechallenge)
    - Dose, pharmacokinetic, immunologic relationships
    - Biologic plausibility

Laboratory event analysis

- Prespecified normal ranges
- Prespecified significant changes
- Summary descriptive statistics
  - Measures of central tendency (e.g., mean)
  - Frequency of shifts to abnormal values
  - Temporal trends
  - Subgroup analyses
- Outlier analyses

Post-marketing safety evaluation

- Goals
  - Definitive evidence of safety/efficacy
  - Safety data from broader population
    - Patients with disease vs. healthy volunteers
    - Special populations (elderly, pediatrics, co-morbidities)
    - Populations receiving concomitant medications
  - PK data from broader population
- Challenges
  - Unpredictable epidemiology of bioterrorism events
  - Difficulties with rapid case ascertainment
  - Difficulties with follow-up
  - Difficulties with protocol implementation
  - Difficulties with information collection

Post-marketing safety studies

- Detailed advance planning is critical
- Careful design of protocols and CRFs
  - Goal is complete, accurate data collection
  - Consider different scenarios (e.g., mass casualty)
  - Consider recommended E/M guidelines
  - Consider likely sites for patient care
  - Consider likely health care providers
  - Consider need to focus on AEs, laboratory data
  - Consider mechanisms for collecting PK data
  - Advance discussions with FDA, other public health agencies
- Consider suggestions in 2004 Draft Guidance: Developing Drugs to Mitigate Complications from Smallpox Vaccination

Summary

- NDA/BLA review centers on risk-benefit ratio
- Design of safety evaluation program based on
  - Preclinical toxicology
  - Intended use
  - Potential population
- Early FDA consultation re: safety program

Guidances

- FDA
  - 2004 Draft Guidance: Premarketing risk assessment
  - 2002 Draft Guidance: Estimating safe starting dose
  - 1997 Points to Consider: monoclonal antibodies
- ICH
  - E2A-E: Clinical safety data management
  - E3: Structure/content of clinical study reports
  - E7: Clinical investigation in the geriatric population
  - E8: General considerations for clinical trials
  - E9: Statistical principles for clinical trials
  - E11: Clinical investigation in the pediatric population